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# Anorectal Lymphoma and AIDS: An Outcome Analysis

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**Background and Objective:** Primary lymphoma of the anus is an extremely rare problem. In patients with the Acquired Immune Deficiency Syndrome (AIDS), there is a marked increase in gastrointestinal non-Hodgkin's lymphomas (NHL). The aim of this study was to evaluate the outcome of patients with anorectal NHL and AIDS.
**Methods:** Over an 18-year period, we identified 6 patients with AIDS and primary anorectal NHL. Five were male. All were high-grade B-cell lymphomas and half showed systemic "B" symptoms. Patient's mean CD4 count was 93 (range 8 to 201).
**Results:** The average life span for those with "B" symptoms was 6.7 months and 16 months for those without symptoms. No benefit was shown from radiation or chemotherapy in those with "B" symptoms. Younger patients and those without systemic constitutional symptoms of lymphoma do better. One patient without "B" symptoms was able to tolerate his radiation and chemotherapy and is disease free at 10 months.
**Conclusion:** Despite traditional non-Hodgkin's lymphoma treatment regimens, our AIDS patients (and those examined in a review of the pertinent literature) with anorectal NHL and "B" symptoms have a poor prognosis. For those without "B" symptoms and who can tolerate the therapy, NHL remission may be obtained.
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KEY WORDS: **non-Hodgkin's lymphoma; AIDS; anus; rectum; CD4 count**

## INTRODUCTION

With the improved survival now found in patients with the acquired immune deficiency syndrome (AIDS), the patterns of associated diseases have also changed. The increased life expectancy is through better treatment of opportunistic infections and improved antiretroviral therapy. Increased life expectancy has resulted in an increased rate of malignant tumors. In particular, lymphomas in AIDS patients have become increasingly frequent. In 1985, the Centers for Disease Control acknowledged this fact by including non-Hodgkin's lymphoma (NHL) occurring in HIV-positive individuals in the definition of AIDS [1]. Non-Hodgkin's lymphoma is the second most common neoplasm behind Kaposi's sarcoma among persons who have AIDS [2].

Lymphomas in AIDS patients are of a higher histologic grade, more aggressive, of B-cell origin, prone to early dissemination, resistant to treatment, and are primarily of extra nodal origin [3]. The central nervous system and the digestive tract are the most frequently affected sites. This makes AIDS-associated lymphomas similar to lymphomas occurring in patients with other forms of immunosuppression. However, only about half of AIDS lymphomas have the Epstein-Barr virus genome while other immune suppressed patients are nearly all positive for the virus [4]. Burkitt's lymphoma is commonly found with AIDS infections but not with other forms of immune suppression.

## MATERIALS AND METHODS

We performed a retrospective review of all anal malignancies at Parkland Memorial Hospital from January

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**TABLE I. AIDS Patients With Anorectal Lymphoma**

| Patient no. | Year diagnosed | Age (years) | Gender | Stage | Survival (months) | CD4 (cells/mL) | Symptoms |
|---|---|---|---|---|---|---|---|
| 1 | 1985 | 36 | M | 2 | 13 | ? | "B" |
| 2 | 1993 | 48 | M | 1 | 5 | 201 | "B" |
| 3 | 1993 | 37 | M | 3 | 3 | 10 | "B" |
| 4 | 1992 | 46 | F | 1 | 21 | 8 | "A" |
| 5 | 1992 | 43 | M | 1 | 10 | 175 | "A" |
| 6 | 1998 | 30 | M | 1 | New diagnosis | 69 | "A" |

? = not drawn.

1980 through December 1998. There were 66 squamous cell carcinoma variants, five cloacogenic carcinomas, and six lymphomas. The six patients with lymphoma also had AIDS and make up the basis for this report (Table I). There were five homosexual males and one female. The average age was 40 (range 30–48). Three of the six presented with "B" symptoms including fevers, night sweats, and/or weight loss. All complained of anal pain. Three presented with an abscess or fistula. Three presented with a mass. All were of B-cell origin. Four were stage 1, one was stage 2, and one was stage 3. Although CD4 counts were not measured in our first patient in 1985, the remaining five had initial CD4 counts ranging from 8 to 201 (all counts are per milliliter) with an average of 93.

## RESULTS

All patients were enrolled to be treated with a regimen of CHOP (cyclophosphamide, actinomycin, vincristine, and corticosteroids) and radiation therapy. The first patient underwent three courses of CHOP but no radiation therapy in 1985. He lived 13 months and died of disseminated lymphoma. A second patient declined treatment and died in 5 months. His CD4 count fell from 201 to 19 before he died. The third patient received only one course of chemotherapy and no radiation therapy. He died in 3 months. His CD4 count fell from 10 to 3. These three patients all suffered "B" symptoms while the next three did not. The fourth patient was the only female patient. She completed two courses of CHOP and 2,500 cGy of radiation therapy before refusing further therapy secondary to persistent fevers and diarrhea. Although her CD4 count at the start of therapy was only 8 and fell to 0 with her chemotherapy, she lived 21 months. The fifth patient had an initial CD4 count of 175 and fell to 20 with treatment. His therapy consisted of three courses of CHOP and 4,000 cGy radiation therapy. Severe thrombocytopenia leading to hemorrhage and the need for multiple transfusions complicated his care. He lived 10 months. The sixth patient was diagnosed 10 months ago and had an initial CD4 count of 69. He received triple antiretroviral therapy with his CD4 count rising to 219 before beginning chemotherapy and radiation therapy. He is currently without evidence of disease. The average life expectancy for those with "B" symptoms was 7 months and for those without symptoms was 15.5 months.

## DISCUSSION

Lymphomas arising primarily in the anorectum are rare occurrences in the population at large, representing only 0.1–1.3% of all malignant rectal lesions [5]. This is probably because usually there is no lymphoid tissue in the anorectum. One theory concerning the development of gastrointestinal lymphomas is that they originate in mucosa-associated lymphoid tissue (MALT) [6]. In homosexual men, the rectum and anus are subject to long-standing infections with various pathologic agents related to receptive anal intercourse. They are thought to have an "acquired" MALT due to these repeated infections and thus have the potential for the origin of lymphoma. Other AIDS patients are also at risk for anal infections due to their compromised immune systems. Antigen receptor gene arrangement analysis has confirmed the B-cell lineage derivation of AIDS associated NHL. However, Southern blot hybridization analysis has consistently failed to find HIV sequences in the genome of AIDS associated NHL and, therefore. no evidence that HIV is directly involved with the malignant B-cells [2]. However, it is possible that there is another virus with oncogenic potential that is enhanced secondary to the immuno-suppression in HIV-infected patients.

Through June 1989, 97,258 cases of AIDS among residents of the United States were reported to the CDC. Non-Hodgkin's lymphoma was identified in 2,824 (2.9%) vs. the expected incidence in the United States of 48. Thus, the risk of NHL in the United States is about 60 times greater in AIDS patients than in the general population [5]. As the total AIDS figure includes females as well as males who have contracted AIDS through non-anal receptive intercourse, the risk is probably higher for male homosexuals. Burkitt's lymphoma was at least 1,000 times more frequent in people with AIDS than in the general population [5].

The median age at diagnosis of AIDS-related NHL is 38 years compared with 56 years for HIV-negative pa-

tients with NHL. More importantly, 65% of AIDS-related NHLs are high grade compared to 10% of HIV-negative [7]. The B-cell lymphomas feature one of three histologic categories: large cell, large cell immunoblastic, and Burkitt's (small noncleaved cell) [8]. There is no difference in outcome among these three types. Multiple chemotherapy regimens have been used with little success. A recent study compared the effect of adding recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) to chemotherapy for AIDS associated NHL but showed no improvement in survival [9].

It has become apparent that critically low CD4 levels markedly increase the risk of NHL. The National Cancer Institute (NCI) has a cohort of 55 AIDS patients with CD4 counts less than 350 (average 74) and expected survival greater than 3 months who were treated with long-term zidovudine (AZT) [10]. Some of the patients were treated with AZT alone (29 patients), some were treated with AZT and acyclovir (8 patients), and some were treated with alternating AZT and 2′,3′-dideoxycytidine (18 patients). They were all treated a minimum of 6 months. Median survival in all patients was 22 months. Eight of the original 55 patients developed NHL. For those patients with NHL, the average CD4 count at the start of AZT therapy was 26 and at diagnosis of lymphoma was 6. The probability for development of NHL in these AIDS patients was 12% after 24 months and 29% after 36 months of continuous zidovudine treatment [11]. In an effort to eliminate AZT as the causative factor for NHL, a placebo-controlled study of patients with asymptomatic HIV infection and CD4 counts above 200 was performed. The addition of AZT was not associated with an increased incidence of NHL [12].

The NCI followed up this study with an evaluation of 61 patients with an average CD4 count of 61 receiving antiretroviral therapy with dideoxyinosine (ddl). In this trial, the estimated probability of developing NHL within 24 months of starting therapy was 6% increasing to 10% at 36 months. Although this figure is lower than the AZT cohort, the difference is not statistically different. This difference may be due to a more sustained increase in the CD4 count from ddl than AZT. A combination of all NCI patients receiving antiretroviral therapy gives an estimated probability of NHL development of 8% at 24 months and 19% at 36 months. The average CD4 count at the time of NHL diagnosis was 11 [11].

There are 33 prior cases reported in the English literature concerning anorectal NHL in AIDS patients [6,13–21]. In those in which the gender is stated (21 patients) all were male. Sixteen presented with a mass and 17 presented with an abscess or fistula. In those that reported the age (21 patients), the average was 38 with a range of 27–54. Ten patients have a reference to chemotherapy, radiation therapy, or both. There is no mention in any of the prior reports of the dose of therapy or completeness of the regimen. CD4 counts are mentioned in only one case report [10] and in none of the series. T4/T8 ratios are listed in 6 patients with a range from 0.07 to 0.40 and average 0.26. Only two series list survival data and both relate to homosexual men ages 35 to 45 [11,12]. Survival in months for the patients with "B" symptoms was 6 months while the patient without "B" symptoms lived 17 months (Table II). A final case from the literature relates to a 44-year-old nonhomosexual man with anorectal lymphoma as his initial AIDS defining illness [22]. His disease is probably unrelated to his HIV status as his tumor is mixed cellularity and is a Hodgkin's lymphoma. Subsequent HIV testing was positive with a CD4 count of 438. Six cycles of chemotherapy were given and the patient is disease free at six months.

**TABLE II. Literature Overview in AIDS Patients With Anorectal Lymphoma**

| Patient no. | Age (years) | Gender | Stage | Survival (months) | T4/T8 ratio | Symptoms |
|---|---|---|---|---|---|---|
| Burke-1 | 37 | M | 1 | 6 | ? | "B" |
| Burke-2 | 45 | M | 4 | 4 | 0.3 | "B" |
| Burke-3 | 36 | M | 4 | 8 | ? | "B" |
| Burke-4 | 35 | M | 1 | 8 | ? | "B" |
| Lee-1 | 35 | M | 1 | 17 | 0.3 | "A" |

? = unknown.

The relationship of CD4 counts to survival of AIDS associated lymphomas is well known. A study of 84 patients with AIDS associated NHL including three of the anorectum looked at the relationship between CD4 counts and survival [10]. In all patients, CD4 counts greater than 100 had a median survival of 24 months while those having CD4 counts of less than 100 had a median survival of 4.1 months. The CD4 count was the most important predictor of survival in that study. Another study evaluated survival in 73 patients with AIDS associated NHL [23]. Their overall survival was 8 months. Thirteen of the 73 patients achieved complete remission at 2 years. These patients had an average CD4 count of 287. This study also found a CD4 count higher than 100 to positively effect survival. In addition, age less than 30 and absence of "B" symptoms positively effected survival. The NCI study reported that patients entered into the AZT treatment arm did not develop NHL until their CD4 counts fell below 50.

Survival from colon and rectal lymphomas without the presence of HIV seropositivity has been dismal. Shepherd examined 45 cases of lymphoma involving the colon and rectum in patients who had no evidence of AIDS [24]. In his study, there were 6 cases of high-grade B-cell lymphomas of the anorectum similar to the type now found in AIDS patients. There is no mention of the presence or absence of constitutional symptoms. They were

treated with a combination of surgery, radiation, and chemotherapy. Only 1 of the six patients was alive and disease free at 2.5 years. The remainder died of their lymphoma at a mean of 21 months (range 8–41 months).

In our patients, CD4 counts did not seem to predict length of survival. One of our patients with a CD4 count above 100 had "B" symptoms at diagnosis and died in 5 months. A subsequent patient with a CD4 count below 100 at diagnosis but no "B" symptoms lived to 21 months. None of our patients were younger than 30. Our patients with "B" symptoms did worse with an average expectancy of 7 months compared to 16 months for the patients who were asymptomatic. In addition, after raising his CD4 count using antiretroviral therapy, our last patient who is without "B" symptoms, was able to tolerate the therapy and appears to have had a complete remission at 10 months.

## CONCLUSION

Based on our patients, it does not seem reasonable to extrapolate the data from reviews of historic AIDS-associated NHL to AIDS-associated anorectal NHL. Survival can be expected to be longer in patients who do not have "B" symptoms. Larger series of AIDS associated NHL also show a survival advantage in patients who are less than thirty years of age and have CD4 counts greater than 100. An increased incidence of NHL may occur from prolongation of life in those AIDS patients with CD4 counts less than 50. Antiretroviral triple drug therapy, which has been shown to increase CD4 counts and prolong generic AIDS survival, may prevent or delay anorectal NHL. At this point, anorectal non-Hodgkin's lymphoma in AIDS patients with critically low CD4 counts or "B" symptoms carries a universally poor prognosis. In those patients who are without "B" symptoms, whose AIDS can be controlled, and those who can tolerate the therapy, remission may be obtained at rates similar to the non–HIV-positive population.

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## COMMENTARY

Place et al. retrospectively reviewed 6 patients with AIDS who also had anorectal non-Hodgkin lymphoma (NHL), a small subset of all anorectal malignancies at Parkland Memorial Hospital. These patients typically are young homosexual males (range: 30–48 years) who present with rectal masses, fistulae, abscesses, and perhaps with "B" symptoms that include night sweats, fever, and/or weight loss.

All 6 patients were relegated to a regimen of CHOP (cyclophosophamide, actinomycin, vincristine, and cor-

tisones) and followed at intervals with radiation therapy. The authors confirmed "B" symptomatology to be a significant risk factor. The short life expectancy of individuals with "B" symptoms (7 months) is at remarkable contrast with those with absent symptoms (15.5 months). When one considers that non-Hodgkin lymphoma is evident in approximately 3% of the AIDS residents in the United States, the importance of the presence of "A" or "B" symptoms is obvious. As indicated, the risk of non-Hodgkin lymphoma in the United States is therefore, approximately 60 times greater for AIDS patients than for those in the general population [1]. The risk is probably highest for male homosexuals, as a consequence of their AIDS-compromised immune systems and sexual practice of receptive anal intercourse. Moreover, Burkitt's lymphoma is at least 1,000 times more frequent in individuals with AIDS than in the general population [1].

Patients with NHL with high average CD4 counts should have better outcomes. Low CD4 counts with the diagnosis of lymphoma carries a dismal prognosis. Individuals being treated for NHL with zidovudine (AZT) should have a CD4 count to evaluate the effectiveness of subsequent therapy and to judge the prognosis of comorbid presentations. Pluda et al. [2] found that the probability for development of NHL in AIDS patients is 12% after 24 months of AZT therapy and 29% after 36 months. Of importance, in a placebo-controlled study that tracked CD4 counts in patients with asymptomatic HIV infections, Volberding et al. [3] determined that the addition of AZT was not associated with an increased incidence of NHL.

To the surgeon, the presentation of a rectal mass with abscess or fistula in a male homosexual patient suspected of AIDS is significant. These individuals are typically male, and should "B" symptoms be evident, poor outcomes are predictable. The relationship of CD4 counts to survival with AIDS-associated lymphoma is well recognized. As in other studies, the authors have concluded that the CD4 count is the most important predictor of survival; their patients with "B" symptoms had overall survival of 4–8 months. Finally, survival of patients with anorectal lymphoma but without HIV symptoms or AIDS is also dismal. Shepherd et al. [4] evaluated several cases of anorectal NHL without AIDS. Despite combination therapy with surgery, radiation, and chemotherapy, only 1 of 6 patients was alive and disease-free at 2.5 years (mean survival was 21 months).

In summary, these data imply that an increased frequency of NHL may occur from prolongation of life in AIDS patients who have CD4 counts $\leqslant 50$. While antiretroviral triple-drug therapy has been noted to increase CD4 counts and prolong generic AIDS survival, its use should be considered, as it may prevent or delay the onset of anorectal NHL. Large series of AIDS-associated NHL have shown a survival advantage in patients with CD4 counts $\geqslant 100$ and for patients $\leqslant 30$ years old. As we will perhaps see an increase in the frequency of NHL as the presentation of AIDS patients in the United States continues to rise, this trend in morbidity and mortality would be expected for those with low CD4 counts. Place et al. properly emphasize that for the patients without these symptoms and in whom the symptomatology of AIDS can be controlled, remission may be obtained at rates similar to the non–HIV-positive population. Despite the dismal survival prospects for "B" symptom patients with low CD4 counts, in my view, triple therapy with surgery, radiation, and chemotherapy is still indicated with antiretroviral triple-drug therapy to attempt to improve symptoms and possibly enhance survival.

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